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Deep Coagulation of Dermal Collagen With Repetitive Er:YAG Laser Irradiation

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Background and Objective: **Er:YAG lasers are known to effectively ablate human skin with minimal thermal damage to subjacent dermal tissue. We have investigated whether deep coagulation of dermal collagen, similar to that observed with the CO_2 laser, could be achieved with repetitive Er:YAG laser exposures.**
Study Design/Materials and Methods: **Skin on the back of a Sprague-Dawley rat in vivo was irradiated with sequences of 1–10 Er:YAG laser pulses at a repetition rate of 10 or 33 Hz and single-pulse fluences from 0.8 to 1.4 J/cm^2. The resulting lesions were biopsied within 1 hour after laser exposure, and the histologic sections were examined by using optical microscopy.**
Results: **The depth of dermal collagen denaturation increases dramatically when 3–10 low-fluence Er:YAG laser pulses are stacked at a repetition rate of 10 or 33 Hz.**
Conclusion: **Coagulation of dermal collagen deeper than 200 μm below the epidermal-dermal junction is feasible by using the appropriate settings of a repetitive Er:YAG laser. Lasers Surg. Med. 26:215–222, 2000.**

Key words: laser skin resurfacing; repetitive laser exposure; collagen denaturation

INTRODUCTION

The Er:YAG laser ($\lambda = 2.94$ μm) is known to ablate effectively human skin with minimal amount of residual thermal damage [1–3]. This results in faster reepithelialization and less-pronounced erythema compared with the deeper penetrating CO_2 lasers [2,4,5]. In clinical laser skin resurfacing (LSR), however, coagulation of collagen in the papillary dermis (100–200 μm below the skin surface), as achieved with CO_2 lasers, is generally believed to be beneficial [6], because it leads to skin tightening/sculpting and formation of new collagen. Here, we demonstrate how a similar effect can be achieved by cumulative tissue heating by using a repetitive Er:YAG laser.

Due to the very strong absorption of Er:YAG radiation in tissue water ($\mu \sim 1{,}000$ mm^{-1}), tissue deeper than ~5 μm below the skin surface is heated exclusively by diffusion of heat from the superficial laser-tissue interaction layer. Therefore, one approach to achieve deep collagen coagulation is to use long laser pulses [7,8]. However, given the limitations of existing laser technology, coagulation depths beyond 30–50 μm are not possible with single-pulse Er:YAG exposure.

Variations in depth of residual thermal damage with complete or partial overlapping of con-

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secutive laser exposures have been previously investigated [3,9–13]. However, those studies were concerned primarily with the efficiency of Er:YAG laser ablation, or safety of CO_2 LSR and other surgical procedures, where a failure to spatially separate subsequent laser pulses might induce excessive thermal damage, potentially resulting in unwanted side effects such as dyspigmentation or scarring.

The potential for deep collagen coagulation by stacking repetitive Er:YAG laser pulses on the same tissue site has been described earlier by simple analytical [14] and more complex numerical modeling. One numerical model of pulsed Er:YAG laser exposure of human skin [15,16] predicted a 10-fold increase in the collagen coagulation depth, from 18 μm with a single-pulse irradiation to 165 and 195 μm with a sequence of 10 subablative pulses (fluence 0.6 J/cm^2, duration 300 μs), delivered at a repetition rate of 10 and 50 Hz, respectively [15,16]. To our knowledge, these predictions have not been tested to date in an in vivo study.

MATERIALS AND METHODS

A Sprague-Dawley female rat (300 g) was used as the in vivo animal model. After being housed in a pathogen-free animal facility and fed a commercial base diet and water ad libitum, the rat was anesthetized with an intraperitoneal injection of ketamine (87 mg/kg) and xylazine (13 mg/kg). A total of 10 lesions were induced on the animal's shaved back by using a dermatologic Er:YAG laser (UltraFine by Coherent, Santa Clara, CA). Each location was irradiated with a sequence of 1 to 10 laser pulses at a repetition rate of 10 or 33 Hz. A nominally 4-mm handpiece was mounted 25 cm above the target skin surface to increase the spot size. By scanning a pyroelectric detector with a 0.62-mm diameter pinhole across the laser spot, the single-pulse fluence (energy density) was measured to be within 1.4 ± 0.2 J/cm^2 in the central 3.4 mm of the 3.9-mm diameter (at half maximum) spot at repetition rate of 10 Hz. For some lesions, one or two external attenuators were used to further decrease the fluence to approximately 1.1 and 0.8 J/cm^2, respectively.

Tissue samples were taken from the laser-induced lesions and a control location by using a 4-mm punch biopsy (Miltex, Lake Success, NY) within 1 hour after the laser exposure. Histologic sections (6 μm) perpendicular to the skin surface were stained with regressive hematoxylin and eosin (H&E). Two examiners, blind to the protocol, used an optical microscope (Olympus, model BH-2) with a reticule eyepiece to assess the thickness of the remaining epidermis and the depth of thermal injury (measured from the epidermal-dermal junction). The values presented below are the averages of the depths assessed by both investigators from 7 to 42 ($\bar{n} = 19 \pm 10$) histologic sections for each lesion. The error intervals and bars always represent the standard error of the mean.

In analyzing the histologic sections, the regressive H&E stain helps determine the coagulation depth by a change of hue from red to purple for thermally denatured dermal collagen. Also, distinct changes in dermal morphology can be observed in thermally damaged tissue. Normal dermis is made up of irregular collagen fibers and fibroblasts having an orientation roughly parallel to the skin surface. When the skin is thermally damaged, collagen fibers lose their linearity and become fused with their neighbors [17,18]. We use such collagen coagulation or hyalinization (glass-like appearance) as the principal marker to determine the depth of thermal damage. Because the biopsies were taken within 1 hour after laser exposure, inflammatory mediators and other cellular indicators of thermal damage (i.e., polymorphonuclear leukocytes) did not have enough time to develop.

RESULTS

Figure 1a shows a histologic section of a non-irradiated (control) skin location, displaying the reference thickness of normal epidermis and structure of intact dermis in our animal model. In contrast, the site irradiated with a single laser pulse at 1.4 J/cm^2 shows a partly ablated epidermis and a very thin (~12 μm) superficial layer of thermally damaged dermis, which is identified by collagen coagulation (marked with an arrow in Fig. 1b).

The histology in Figure 1c demonstrates the significantly increased depth of collagen coagulation (~280 μm, see the arrow), resulting from a sequence of 5 pulses at the same single-pulse fluence (1.4 J/cm^2) and repetition rate of 33 Hz. The collagen coagulation pattern is somewhat nonhomogeneous and patchy in appearance, similar to that observed in most other histologic sections in this study. The transition from coagulated to normal collagen structure deeper in the dermis is very gradual. Note also hyperchromasia in the

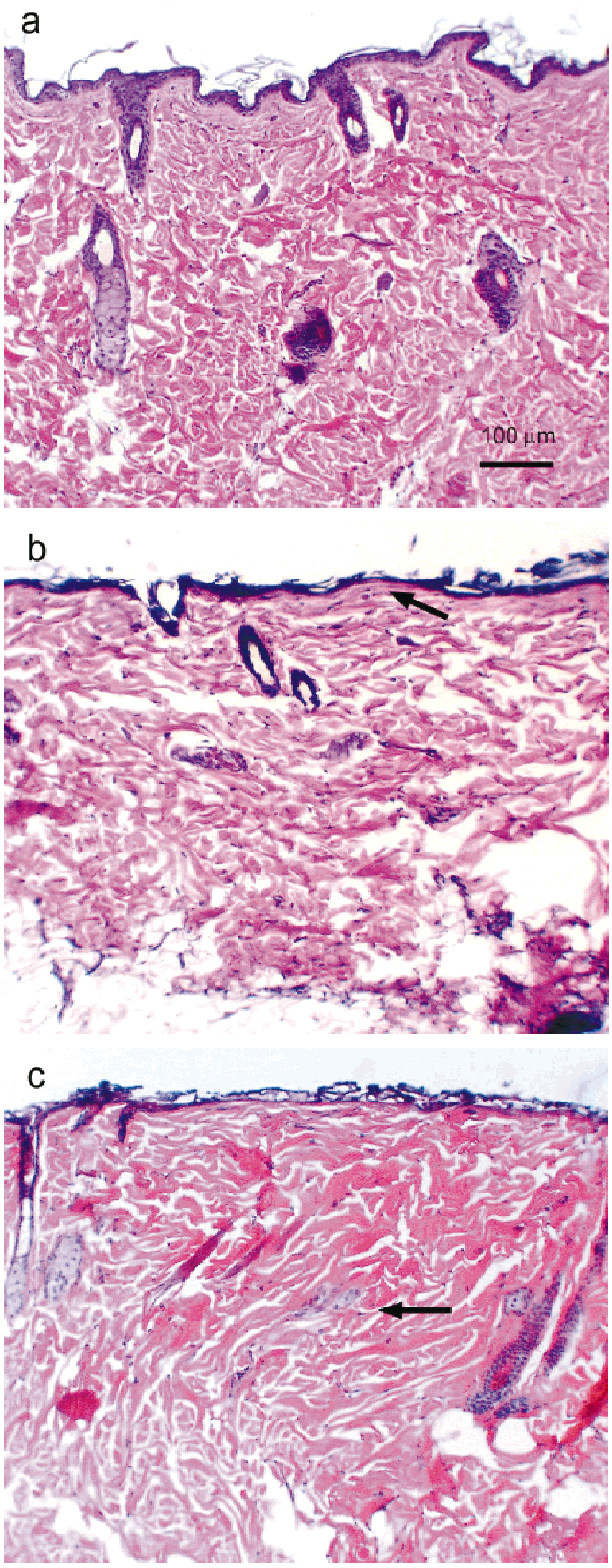

Fig. 1. **a:** Histologic section of nonirradiated skin (control). **b:** Single-pulse lesion (fluence $F = 1.4$ J/cm^2) demonstrating a minimal amount of thermal damage to the dermis (see the arrow) and minimal epidermal ablation. **c:** Arrow indicates the significantly increased depth of collagen coagulation (~280 μm) resulting from a sequence of five pulses (1.4 J/cm^2, 33 Hz). The scale in these and all subsequent photographs matches that indicated by the bar in Figure 1a (100 μm length). Original magnification, ×200.

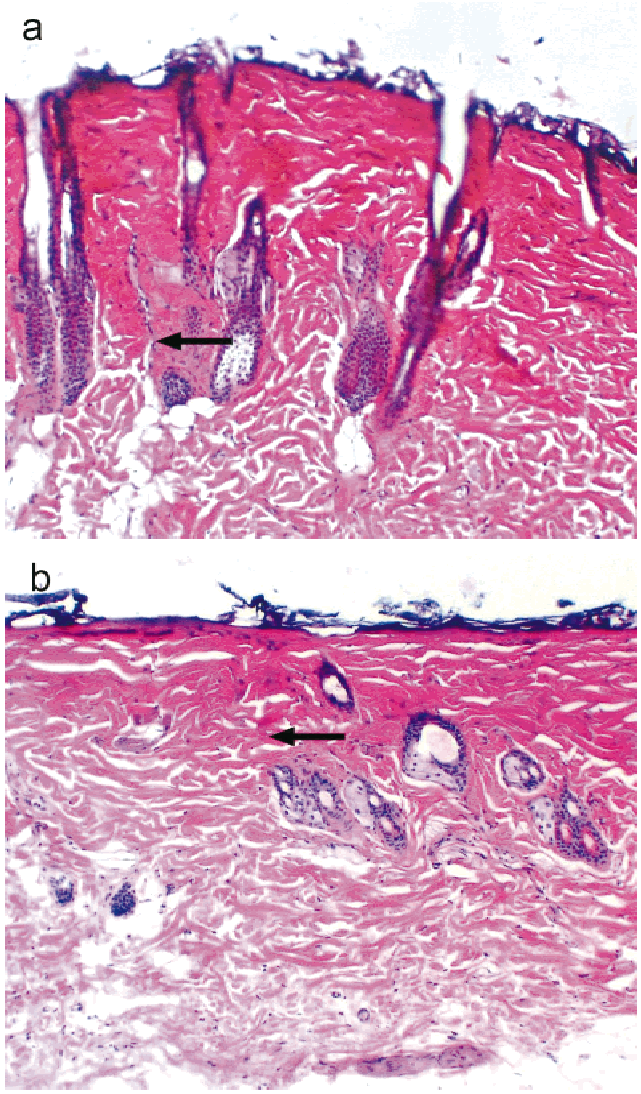

Fig. 2. **a:** Extremely deep collagen coagulation (~350 μm, see the arrow) as obtained with 10 pulses at a lower fluence (1.1 J/cm^2, 10 Hz). **b:** With even lower fluence (0.8 J/cm^2), more epidermis is preserved, whereas the coagulation layer is still relatively thick (arrow; 10 pulses at 10 Hz).

hair follicle epithelium, indicating superficial thermal damage, and more pronounced ablation of the epidermis compared with Figure 1b.

Figure 2a shows even more extensive collagen coagulation (~350 μm, see the arrow) obtained with a sequence of 10 pulses at a lower fluence (1.1 J/cm^2, 10 Hz), as evidenced by the classic hyalinized appearance. The epidermis in this lesion is almost completely ablated. When an even lower single-pulse fluence of 0.8 J/cm^2 is used (Fig. 2b, 10 pulses at 10 Hz), the epidermis is ablated to a lesser extent, whereas the coagulation layer is still relatively thick. Several intact

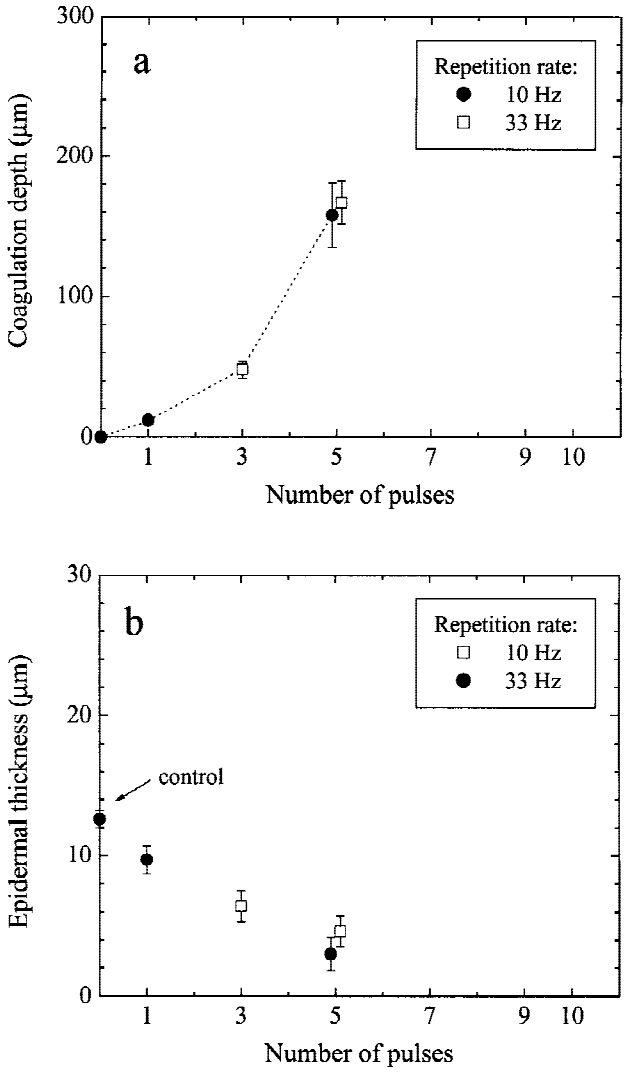

Fig. 3. **a:** Average depth of dermal thermal damage (measured from the epidermal-dermal junction) as a function of number of pulses in the exposure sequence. Single-pulse fluence is 1.4 J/cm^2, pulse repetition rate is either 10 Hz or 33 Hz. **b:** Thickness of epidermis remaining after the laser exposure at the same conditions. Error bars mark the standard error of the mean.

hair follicles can be seen in the region of normal dermis below the thermally damaged collagen.

An overview of the average collagen coagulation depths and the remaining epidermal thicknesses, obtained by stacking a varying number of 1.4 J/cm^2 pulses on the same site, is presented in Figure 3a and b, respectively. The pulse repetition rate used was 10 (closed) or 33 Hz (open symbols). Note that the results obtained with the single-pulse irradiation are common to both data sets. The same is true for the nonirradiated control sample, which helps determine the reference epidermal thickness of 12.6 ± 0.6 μm (n = 15). With the single-pulse irradiation, the thickness of the thermally damaged dermis is estimated at 12 ± 3 μm, measured from the epidermal-dermal junction, and the remaining epidermal thickness is 9.7 ± 1.0 μm (n = 21).

As the number of laser pulses in a sequence increases, the amount of thermal damage increases unproportionally (Fig. 3a), reaching 158 ± 23 μm and 167 ± 15 μm with 5 pulses at repetition rates of 10 and 33 Hz, respectively. Meanwhile, the epidermal thickness decreases nearly linearly with the number of stacked pulses, possibly indicating a minor reduction of ablation efficiency with increasing number of pulses (Fig. 3b). The differences between the results obtained with repetition rates of 10 and 33 Hz are within the experimental error.

Dermal coagulation depths and remaining epidermal thicknesses, obtained with a lower single-pulse energy density of ~1.1 J/cm^2, are presented in Figure 4. The coagulation depths are greater than those obtained with 1.4 J/cm^2 pulses and begin to saturate at a depth around 200 μm, which is reached with 3–5 pulses. The remaining epidermal thickness decreases in a similar manner as in the previous example, but indicates a larger reduction of ablation efficiency at higher numbers of pulses. As above, the results obtained with the two repetition rates do not differ significantly.

Figure 4a,b displays also the results obtained with a sequence of 10 pulses with an even lower single-pulse fluence of ~0.8 J/cm^2 and repetition rate of 10 Hz (star symbol). The dermal coagulation depth is reduced in comparison to the previous example, but still relatively deep at 140 ± 18 μm (n = 16), whereas approximately half of the original epidermal thickness is preserved (6.8 ± 1.8 μm).

DISCUSSION

In many histologic sections indicating deep thermal damage, the observed collagen coagulation pattern was nonhomogeneous and somewhat patchy. In addition to the nonhomogeneity of skin, this could be attributed in part to the characteristic rings and "hot spots" in the hat-top lateral beam profile of the Er:YAG laser, which may evade our rough profile evaluation but do show up on the photographic paper. These nonuniformities tended to be more pronounced at repetition rate of 33 Hz, where somewhat higher fluence values of 1.5 ± 0.3 J/cm^2 were found in the central 3.3 mm

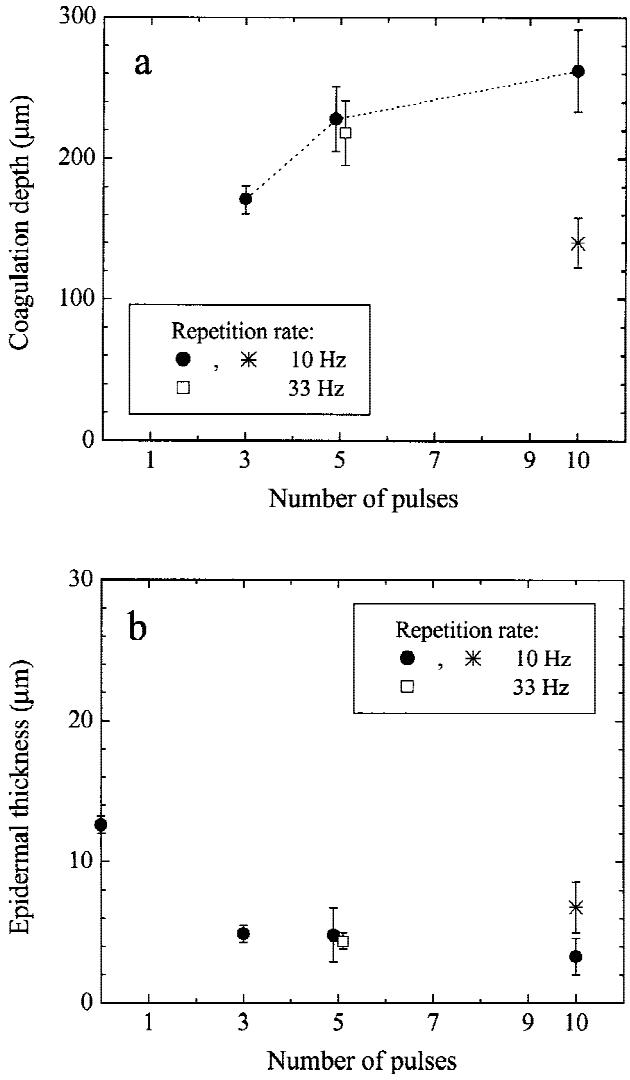

Fig. 4. Same as Figure 3a,b but with a single-pulse fluence of 1.1 J/cm^2. The results marked with a star were obtained with a single-pulse fluence of 0.8 J/cm^2 and 10 Hz repetition rate.

of the slightly smaller laser spot (3.6 mm diameter at half maximum), compared with the 10 Hz repetition rate. In view of inaccuracies of our beam profile analysis and coagulation depth assessment, we chose to simplify presentation of data by neglecting this difference.

The assessment of coagulation depth was complicated further by the very gradual transition between the coagulated and normal collagen deeper in the dermis. This observation corresponds well to that of Ross et al. [13], who recently reported a broad transition zone when stacking three CO_2 laser pulses (13 J/cm^2, 2 Hz), in contrast with an abrupt transition from denatured to intact collagen in single-pulse thermal damage. Our two examiners were asked to report the effective depth of collagen coagulation in the most damaged part of each histologic section, and use the same criterion throughout the analysis. Our attempt to use optical polarization microscopy (with crossed mica polarizers) to help determine this boundary was not successful, attributable in part to poor contrast between the coagulated zone and intact dermis. This could be attributed to the small thickness of the histologic sections, randomness in collagen fibril orientation in dermis, and an incomplete loss of birefringence in the coagulated zone.

This preliminary study was aimed at proving the feasibility of deep coagulation by using repetitive Er:YAG laser exposures, rather than establishing the exact depths of residual thermal damage, which extends over both coagulation and transition zones [13]. The reported collagen coagulation depths, thus, present a lower estimate of the residual thermal damage. A more accurate assessment of location and specifics of the transition zone would require other experimental approaches, such as quantitative retardance imaging or transmission electron microscopy.

On a number of histologic sections that showed especially nonhomogeneous thermal damage, we observed that the regions of greatest collagen coagulation were invariably around the hair follicles. Figure 5 presents one such example, where most of the collagen is normal except for the area surrounding a large hair follicle, resulting in a peculiar pattern of thermal damage (10 pulses at 1.4 J/cm^2 and 10 Hz). Although the mechanism responsible for this effect remains unclear, the observed pattern resembles the effect of "energy spreading" along the natural cleavage planes in the tissue, as described recently by Fulton and Shitabata for CO_2 LSR [19]. A cleavage plane can be any tissue junction where a basement membrane exists, such as the epidermal-dermal junction, or around the epithelium that surrounds hair follicles or other skin appendages. To our understanding, the irradiated tissue tends to buckle along these cleavage planes as pressure builds up because of overheating of trapped tissue water, thus allowing the pressurized hot vapor to reach areas far outside the laser-tissue interaction volume. This is further supported by the fact that this effect is more pronounced at higher pulse fluences. Such a scenario corresponds well to the microscopic model of laser-tissue interaction used in the aforementioned numerical model of Er:YAG laser skin resurfacing [15,16].

The observed nonlinear increase of coagula-

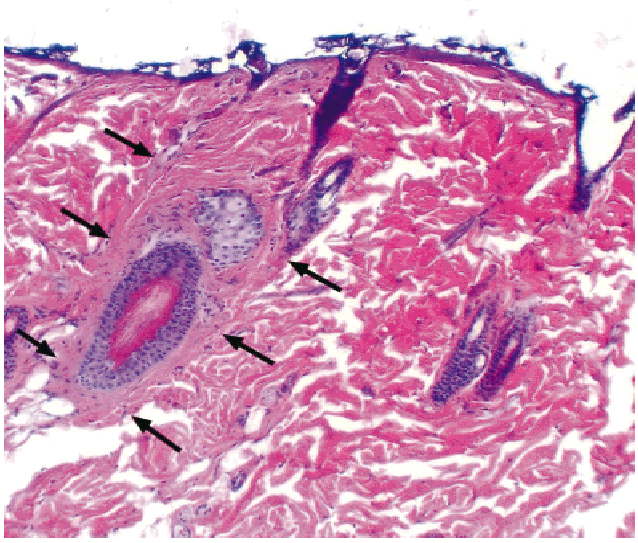

Fig. 5. Excessive collagen damage around the hair follicles (marked by arrows), possibly caused by effect of "energy spreading" along the natural cleavage plane (10 pulses at 1.4 J/cm^2 and 10 Hz).

tion depth with the number of stacked pulses presented in Figure 3a matches qualitatively that predicted theoretically by using the same model [15,16]. The nonlinearity of this dependence reflects the complexity of both the heat diffusion and collagen coagulation process. Given the relative simplicity of the model on one hand, and arbitrary nature in determination of coagulation depths from histologic sections on the other, a better quantitative match could hardly be expected. For the single-pulse exposure (fluence 0.6 J/cm^2, duration 300 μs), for example, the model predicted a coagulation depth of 18 μm, significantly thicker than our observation of 12 ± 3 μm (Fig. 3b). However, the pulse fluence used in the discussed example was significantly higher (1.4 J/cm^2), whereas the presence of epidermal ablation may have diminished deposition of heat during laser exposure. Furthermore, the coagulation depths reported here are measured from the epidermal-dermal junction, in contrast to the total depth from the (nonablated) skin surface, calculated by the model. For the laser pulse duration of 200 μs, used in our experiments, the model predicted the ablation threshold aroung 0.7 J/cm^2, and the maximal residual thermal damage of 22 μm, which incidentally matches the sum of the residual epidermal thickness and coagulation depth observed at 1.4 J/cm^2.

With an increasing number of stacked pulses, the coagulation depth obtained with 1.4 J/cm^2 pulses increases even faster than predicted by numerical modeling. In addition to the abovementioned discrepancies between the laser parameters used in the model and our experiments, this difference could result in part from inaccurate values of the Arrhenius coefficients for collagen coagulation assumed in the model [20]. Further studies on in vivo skin are needed to clarify this issue.

At the lower pulse fluence of 1.1 J/cm^2, coagulation was observed to extend deeper than at 1.4 J/cm^2. This finding has been predicted theoretically for the ablation regime [7,8,21] and can be explained by the reduced ablation efficiency at lower fluences, which results in a larger deposition of heat in tissue underneath the ablation crater. This effect is most likely exaggerated by thermal buildup during the high-repetition-rate irradiation sequence, which desiccates the tissue between subsequent laser pulses and deprives it of the main chromophore for Er:YAG laser radiation [11]. As a result, the ablation efficiency is decreased, as indicated by the results in Figures 3b and 4b, which enhances deposition of heat. Additionally, the optical penetration depth is enlarged, which inherently increases the zone of thermal injury.

With further reduction of single-pulse fluence to 0.8 J/cm^2, the coagulation depth is decreased compared with the previous example (Fig. 4a). This finding can be understood by recalling that the ablation threshold of skin for the Er:YAG laser is usually reported to be around 1 J/cm^2 [5,11,22,23]. At pulse fluences below this value, the amount of thermal damage is expected to decrease with decreasing fluence (in direct proportion, as predicted by the numerical model). That the epidermis was partly ablated at this low fluence (Fig. 4b) can be attributed to thermal buildup with rapid stacking of 10 pulses and/or the relatively short pulse duration, both of which decrease the ablation threshold [15,16]. Nevertheless, nearly half of the initial epidermal thickness was preserved in the example presented, which would aid the healing process after LSR. By further decreasing the laser pulse fluence, perhaps in combination with higher repetition rates, longer pulse sequences, or both, it might be possible to achieve sufficient collagen coagulation depths (100–200 μm) while preserving the epidermis, as suggested by numerical modeling (with ten 300-μs pulses at 0.6 J/cm^2 and 10–50 Hz).

No significant difference between the results obtained with a repetition rate of 10 or 33 Hz was observed at any of the laser pulse parameters

tested. Although this result is somewhat counterintuitive, such an effect could have been anticipated from the numerical model [15,16], which indicated that coagulation depths achieved with increasing repetition rates saturated at a value approximately equal to the single-pulse coagulation depth multiplied by the number of pulses in the sequence. The tentative interpretation of these results by Majaron et al. [16] was that, above a certain repetition rate, the irradiation sequence becomes so short that all deposited heat is confined to a more superficial layer than the final coagulation depth. This finding was illustrated by the corresponding temperature profiles, and further supported by the predicted proportionality of coagulation depth with the number of pulses at a high repetition rate (50 Hz), very similar to the linear fluence dependence predicted for a single subablative pulse.

As an example, a five-pulse sequence at a repetition rate of 10 Hz lasts 0.5 seconds and results in a characteristic depth of heat diffusion around $(Dt)^{1/2} \approx 230$ μm, which corresponds well to the observed coagulation depth at such parameters (Fig. 4a). At the faster repetition rate (33 Hz), the deposited heat is confined to an even more superficial layer and causes a similar amount of thermal damage when diffusing deeper into the skin. The saturation of coagulation depth with increasing number of applied pulses, as seen in the same graph (Fig. 4a), can most probably be attributed to the same or similar effect.

CONCLUSION

Experiments that use an in vivo rat model demonstrate that the depth of dermal collagen coagulation increases dramatically when 3–10 low-fluence Er:YAG laser pulses are stacked on the same tissue location at a relatively high repetition rate (10 or 33 Hz). Histologic investigation shows collagen coagulation as deep as 300 μm below the epidermal-dermal junction, compared with 12 μm observed on the average with a single-pulse exposure. The observed effects and trends correspond well to predictions of a previously published numerical model. In summary, coagulation of collagen deeper than 200 μm below the epidermal-dermal junction in human skin seems feasible by using the appropriate settings of a repetitive Er:YAG laser.

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